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U1S S2410

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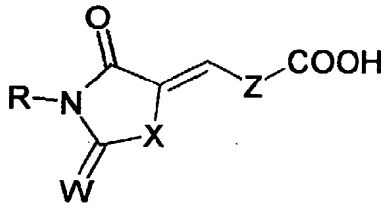
Bollettino Chimico Farmaceutico, 1997, Vol. 136(8), pages 561-567 & Chemical Abstracts, abstr no 132:273866

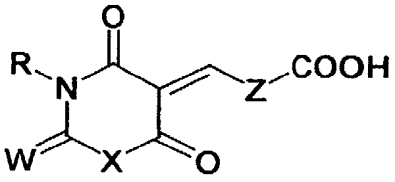
(56) and (58) continued overleaf

(54) Abstract Title
**Carboxy containing (phenyl-/heterocyclyl-)methylene substituted azole & azine derivatives and their therapeutic use as antibacterials**

(57) Compounds of Formula 1



Formula 1a



Formula 1b

[wherein W is S or O; X is NH, S or O; Z is one or more phenyl or heterocyclyl rings (optionally substituted by $C_{1-6}$ alkyl, halogen, hydroxy, alkoxy, nitro and trifluoromethyl) optionally separated by a spacing group $(Y)_n$ where Y is selected from $CH_2$, O, NH, S, S(O), $S(O)_2$ and n = 0 to 6; and R is hydrogen, a phenyl or heterocyclyl ring (optionally substituted by $C_{1-6}$ alkyl, halogen, hydroxy, alkoxy, nitro and trifluoromethyl) optionally separated by a spacing group $(Y)_n$ where Y is selected from $CH_2$, O, NH, S, S(O), $S(O)_2$ and n = 0 to 6, alternatively, R is of the form $(Y)_nCOOH$]
inhibit the phosphopantetheine adenylyltransferase enzyme and may be used as antibacterial agents, eg to treat infections caused by gram positive organisms such as S. aureus.

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(56) cont
**Farmatsevtichnii Zhurnal (Kiev), 1983, Vol. (6), pages 32-34 & Chemical Abstracts, abstr no 100:191772**

(58) Field of Search
Other: **CAS ONLINE**

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# COMPOUNDS AND THEIR THERAPEUTIC USE

## Field of the Invention

This invention relates to compounds, and more specifically to azole or barbiturate analogues, and to their therapeutic use.

## Background to the Invention

Several chemical classes of compound are known that possess considerable antibacterial activity, and these have proven of immense value in the treatment of bacterial diseases and infection. They include among others, the penicillins, the cephalosporins, the aminoglycoside antibiotics, vancomycin analogues and the sulfonamide drugs.

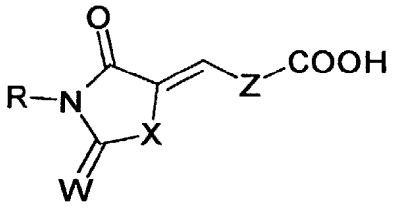
The mechanism of action of a number of known antibiotics is by the direct inhibition of enzymes of essential bacterial biosynthetic pathways. These include, amongst others, trimethoprim and the sulfonamide drugs.

An enzyme of the Coenzyme A biosynthetic pathway, phosphopantetheine adenylyltransferase (PPAT), has been shown to be essential for bacterial viability (WO/ 0017387) and a compound that could inhibit such an enzyme *in vivo* would be likely to be of use as an antibacterial agent.

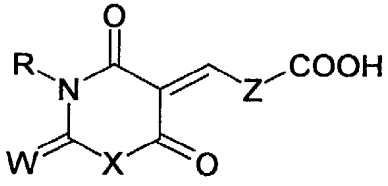
The compounds described in the invention are structurally distinct from previously prescribed antibiotics, and their mode of action is also dissimilar.

## Summary of the Invention

This invention relates to compounds, and more specifically to azole or barbiturate analogues defined by Formula 1a and 1b and to their therapeutic use. The compounds and their pharmaceutically acceptable salts are claimed as the active ingredients in medicines for the treatment of bacterial infection in man and animals.



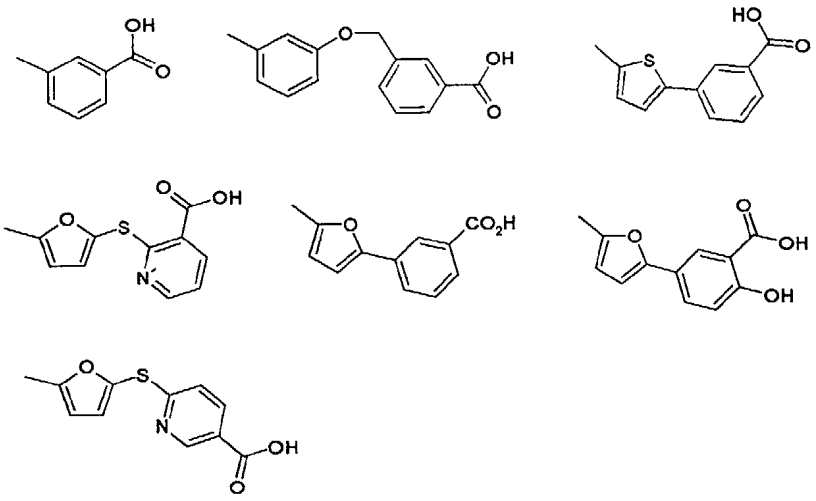

Formula 1a




Formula 1b

wherein W is S or O; X is NH, S or O; Z is one or more phenyl or heterocyclyl rings (optionally substituted by $C_{1-6}$ alkyl, halogen, hydroxy, alkoxy, nitro and trifluoromethyl) optionally separated by a spacing group $(Y)_n$ where Y is selected from $CH_2$, O, NH, S, S(O), $S(O)_2$ and n = 0 to 6; and R is hydrogen, a phenyl or heterocyclyl ring (optionally substituted by $C_{1-6}$ alkyl, halogen, hydroxy, alkoxy, nitro and trifluoromethyl) optionally separated by a spacing group $(Y)_n$ where Y is selected from $CH_2$, O, NH, S, S(O), $S(O)_2$ and n = 0 to 6, alternatively, R is of the form $(Y)_nCOOH$. Compounds of the invention include salts thereof.

Preferred compounds are where R is benzothiazole, m-chlorophenyl, p-(trifluoromethyl)benzyl, benzimidazole, hydrogen or $CH_2COOH$; X is NH, S or O; W is S or O and Z-COOH is:



Compounds of the invention, most of which are new, have therapeutic utility. In particular, they exhibit inhibition of the enzyme phosphopantetheine adenylyltransferase. The compounds are useful as active ingredients in medicines, for the treatment of bacterial infection in man and animals.

Compounds of similar structure to those of the invention have been described before as antibacterial agents. However, these compounds do not contain a carboxylic acid moiety and possess only weak activity. For this reason, the increased antibacterial potency of azole or barbiturate analogues containing a carboxylic acid moiety could not have been predicted and is therefore novel. A number of these compound have been purchased and found to be inactive in our phosphopantetheine adenylyltransferase and only feebly active in our antibacterial screens.

**Description of the Invention**

The term "$C_{1-6}$ alkyl" as used herein refers to straight and branched chain alkyl groups having up to 6 C atoms. Examples are methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl and tert-butyl. "Alkyl" may have the same meaning. "Halogen" means F, Cl, Br or I. "Alkoxy" means $C_{1-6}$ alkyl-O-. "Heterocyclyl" means a saturated, unsaturated or aromatic ring of 5 to 8 atoms containing one or more heteroatoms such as O, S or N, and which may be bonded *via* any C or ring atom.

Compounds of formula 1 may contain one or more chiral centres and exist in optically active forms. When a compound of formula 1 or a salt thereof contains a single chiral centre (for example sec-butyl) it may exist in two enantiomeric forms. The present invention includes individual enantiomers and mixtures of these enantiomers. The enantiomers may be obtained by methods known to those skilled in the art. Such methods typically include resolution via formation of diastereomeric salts or complexes which may be separated, for example, by crystallisation; resolution via formation of diastereomeric derivatives or complexes which may be separated, for example, by crystallisation, gas-liquid or liquid chromatography; selective reaction with one enantiomer by reaction with an enantiomer-specific reagent, for example, enzymatic esterification, oxidation or reduction, followed by separation of the modified and unmodified enantiomers; or gas-liquid or liquid chromatography on a chiral support such as silica with a bound chiral ligand or in the presence of a chiral solvent. It will be appreciated that where the desired enantiomer is converted into another chemical entity by one of the separation processes described above, at least one further step will subsequently be required to liberate the desired enantiomeric form. Alternatively, specific enantiomers may be synthesised by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer into another by asymmetric transformation.

When a compound of formula 1 or a salt thereof contains more than one chiral centre it may exist in diastereomeric forms. The diastereomeric pairs may be separated by methods known to those skilled in the art, for example, chromatography or crystallisation and the individual enantiomers within each pair may be separated as described above. The present invention includes each diastereomer of compounds of formula 1 and mixtures thereof.

Some compounds of formula 1 may exist in the form of solvates, for example, hydrates, which also fall within the scope of the present invention.

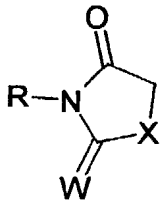
The compounds of formula 1 may form organic or inorganic salts, for example, the compounds of formula 1 may form addition salts with inorganic or organic acids, e.g. hydrochloric acid, hydrobromic acid, fumaric acid, tartaric acid, citric acid, sulfuric acid, hydiodic acid, maleic acid acetic acid, succinic acid, benzoic acid, pamoic acid, palmitic acid, dodecanoic acid and acidic amino-acids such as glutamic acid. Such compounds of formula 1 may form base addition salts, for example, with alkali metal hydroxides e.g. sodium hydroxide, with amino-acids e.g. lysine or arginine or with organic bases e.g. meglumaine. It will be appreciated that such salts, provided that they are pharmaceutically acceptable may be used in therapy in place of compounds of formula 1. Such salts are prepared by reacting the compound of formula 1 with a suitable acid or base in a conventional manner. Such salts may also exist in the form of solvates, for example, hydrates. The present invention includes each salt and any solvate thereof.

Certain compounds of formula 1 or salts thereof may exist in more than one crystal form and the present invention includes each crystal form and mixtures thereof.

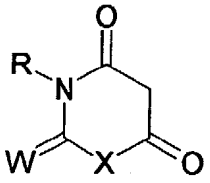
"Pharmaceutically acceptable salts" are acid addition salts which can be prepared by any of the art recognised means. Typical acid addition salts include hydrochloride, hydrobromide, hydroiodide, sulphate, phosphate, acetate, propionate, lactate, malate, succinate, tartrate, cyclohexanesulphamates, methanesulphonates, ethanesulphonates, benzenesulphonates, toluenesulphonates, fumarates and other pharmaceutically acceptable counter ions for amines.

The preferred procedure for preparing compounds of the invention comprises reacting a azole or barbiturate analogue of the formula 2a or 2b with an aldehyde of formula 3, wherein W, X, Z and R are as defined in previously. The reaction can be carried out at a temperature range between -80° to 250°C, optionally in the presence of an acid, base or dehydrating agent, and optionally in the presence of an inert organic solvent. It is appreciated that work-up procedures may involve the use of an acid or base.

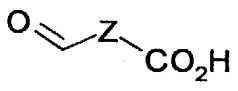
In a preferred method, the reaction is carried out in boiling acetic anhydride as solvent, containing a catalytic amount of sodium acetate.




Formula 2a




Formula 2b




Formula 3

The reactions described herein will be generally understood by one of ordinary skill in the art. The starting materials are available or can readily be prepared by one of ordinary skill in the art.

Compounds of this invention have therapeutic utility, as antibacterial agents. They are especially useful for the treatment of infections caused by gram positive organisms such as *S. aureus*. Without wishing to be bound by theory, their activity may be due to their ability to inhibit an enzyme of the Coenzyme A biosynthetic pathway, phosphopantetheine adenylyltransferase (PPAT). This enzyme has been shown to be essential for bacterial viability (WO-A-00/17387). An assay for activity against PPAT is described below.

The present invention also provides pharmaceutical compositions containing a therapeutically effective amount of a compound of formula I including pharmaceutically acceptable salts thereof together with a pharmaceutically acceptable diluent or carrier

As used hereinafter, the term "active compound" denotes a compound of formula I including pharmaceutically acceptable salts thereof. In therapeutic use, the active compound may be administered orally, rectally, parenterally, topically, ocularly, aurally, nasally, intravaginally or to the buccal cavity, to give a local and/or systemic effect. Thus the therapeutic compositions of the present invention may take the form of any of the known pharmaceutical compositions for such methods of administration. The compositions may be formulated in a manner known to those skilled in the art so as to give a controlled release, for example rapid release or sustained release, of the compounds of the present invention. Pharmaceutically acceptable carriers suitable for use in such compositions are well known in the art of pharmacy. The compositions of the invention may contain 0.1-99% by weight of active compound. The compositions of the invention are generally prepared in unit dosage form. Preferably the unit dosage of active ingredient is 1-500 mg. The excipients used in the preparation of these compositions are the excipients known in the pharmacist's art.

Compositions for oral administration are preferred compositions of the invention and there are known pharmaceutical forms for such administration, for example tablets, capsules, granules, syrups and aqueous or oily suspensions.

Tablets may be prepared from a mixture of the active compound with fillers such as lactose or calcium phosphate, disintegrating agents, for example maize starch, lubricating agents, for example magnesium stearate, binders for example microcrystalline cellulose or polyvinyl pyrrolidone and other optional ingredients known in the art to permit tableting the mixture by known methods. The tablets may, if desired, be coated using known methods and excipients which may include enteric coating using for example hydroxypropylmethylcellulose phthalate. The tablets may be formulated in a manner known to those skilled in the art so as to give a sustained release of the compounds of the present invention. Such tablets may, if desired, be provided with enteric coatings by known methods, for example by the use of cellulose acetate phthalate.

Similarly, capsules, for example hard or soft gelatin capsules, containing the active compound with or without added excipients, may be prepared by known methods and if desired, provided with enteric coatings in a known manner. The tablets and capsules may conveniently each contain 0.1 to 1000 mg (for example 10 mg, 50 mg, 100 mg, 200 mg, 400 mg, 600 mg, or 800 mg) of the active compound. Other compositions for oral administration include, for example, aqueous suspensions containing the active compound in an aqueous medium in the presence of a non-toxic suspending agent such as sodium carboxymethylcellulose, and oily suspensions containing a compound of the present invention in a suitable vegetable oil, for example sunflower oil.

The active compound may be formulated into granules with or without additional excipients. The granules may be ingested directly by the patient or they may be added to a suitable liquid carrier (for example water) before ingestion. The granules may contain disintegrants (for example a pharmaceutically acceptable effervescent couple formed from an acid and a carbonate or bicarbonate salt) to facilitate dispersion in the liquid medium.

Compositions for topical administration are also preferred compositions of the invention. The pharmaceutically active compound may be dispersed in a pharmaceutically acceptable cream, ointment or gel. A suitable cream may be prepared by incorporating the active compound in a topical vehicle such as petrolatum and/or light liquid paraffin, dispersed in an aqueous medium using surfactants. An ointment

may be prepared by mixing the active compound with a topical vehicle such as a mineral oil, petrolatum and/or a wax e.g. paraffin wax or beeswax. A gel may be prepared by mixing the active compound with a topical vehicle comprising a gelling agent e.g. basified Carbomer BP, in the presence of water. Topically administrable compositions may also comprise a matrix in which the pharmaceutically active compounds of the present invention are dispersed so that the compounds are held in contact with the skin in order to administer the compounds transdermally. A suitable transdermal composition may be prepared by mixing the pharmaceutically active compound with a topical vehicle, such as described above, together with a potential transdermal accelerate such as dimethyl sulphoxide or propylene glycol.

Compositions of the invention suitable for rectal administration are known pharmaceutical forms for such administration, for example suppositories with hard fat, synthetic glycerides or polyethylene glycol bases.

Compositions of the invention suitable for parenteral administration are known pharmaceutical forms for such administration, for example sterile suspensions or sterile solutions in a suitable solvent.

Compositions of the invention suitable for inhalation via the mouth and/or the nose are the known pharmaceutical forms for such administration, for example aerosols, nebulised solutions or powders. Metered dose systems, known to those skilled in the art, may be used.

Compositions suitable for application to the buccal cavity include slow dissolving tablets, troches, chewing gum, gels, pastes, powders, mouthwashes or rinses.

The compounds of the present invention may also be administered by continuous infusion either from an external source, for example by intravenous infusion, or from a source of the compound placed within the body, internal sources include implanted reservoirs containing the compound to be infused which is continuously released for example by osmosis and implants which may be a) liquid such as an oily solution or suspension of the compound to be infused for example in the form of a very sparingly water-soluble derivative such as a dodecanoate salt or b) solid in the form of an implanted support for example of a synthetic resin of waxy material for the compound to be infused. The support may be a single body containing all the compound or a series of several bodies each containing part of the compound to be delivered.

In some formulations it may be beneficial to use the compounds of the present invention in the form of particles of very small size, for example as obtained by fluid energy milling.

The following examples illustrate the invention. The intermediates illustrate the preparation of precursors.

Where intermediates are novel, they also form part of the patent.

**Intermediate 1. 3-[(3-Formylphenoxy)methyl]benzoic acid**

To a suspension of 60% sodium hydride in paraffin (2.4 g, 60 mmol) in DMF (15 mL) was added a solution of 3-hydroxybenzaldehyde (3.65 g , 30 mmol) in DMF (15 mL) with effervescence, followed by a solution of 3-(chloromethyl)benzoic acid (5.4 g, 32 mmol) in DMF (15 mL) with effervescence, and the mixture stirred overnight. Water (50 mL) was added and the mixture washed with ethyl acetate (50 mL) to remove the paraffin. The aqueous layer was made acidic with 2M hydrochloric acid (50 mL) and extracted with ethyl acetate (50 mL). The organic layer was washed with brine (2 x 25 mL), then evaporated, to give 3-[(3-formylphenoxy)methyl]benzoic acid (7.4 g, 96% yield).
m/z 279(M+Na), 255(M-H).

**Intermediate 2. 3-(5-Formylthiophen-2-yl)benzoic acid**

To a degassed solution of 5-formylthiophene-2-boronic acid (1.56 g, 10 mmol), 3-bromobenzoic acid (2.0 g, 10 mmol) and sodium acetate (4.0 g, 30 mmol) in 50% aqueous propan-1-ol (20 mL) was added Pd $(PPh_3)_4$ (1.3 g), the mixture degassed then heated to reflux overnight under nitrogen. The mixture was

evaporated, and the residue partitioned between 2M hydrochloric acid (25 mL) and ethyl acetate (25 mL). The mixture was filtered, then the organic layer extracted with 1M sodium hydroxide (25 mL). The aqueous layer was made acidic with 2M hydrochloric acid (25 mL) and extracted with ethyl acetate (25 mL) then filtered. The organic layer was washed with brine (2 x 25 mL), then evaporated, to give 3-(5-formylthiophen-2-yl)benzoic acid (1.1 g, 53% yield).
m/z 233 (M+H), 231 (M-H).

**Intermediate 3. 3-(5-Formylfuran-2-yl)benzoic acid**

3-(5-Formylfuran-2-yl)benzoic acid was prepared from 5-formylfuran-2-boronic acid and 3-bromobenzoic acid according to the method for **Intermediate 2**.
m/z 217 (M+H), 215 (M-H).

**Intermediate 4. 5-(5-Formylthiophen-2-yl)-2-hydroxybenzoic acid**

5-(5-Formylthiophen-2-yl)-2-hydroxybenzoic acid was prepared from 5-formylfuran-2-boronic acid and 5-bromo-2-hydroxybenzoic acid according to the method for **Intermediate 2.**
m/z 249 (M+H), 247 (M-H).

**Intermediate 5. 2-(5-Formylfuran-2-ylthio)nicotinic acid**

To a suspension of 2-mercaptonicotinic acid (8.85 g, 57 mmol) in DMF (50 mL), under nitrogen, was added a solution of potassium hydroxide (6.38 g 114 mmol) in water (10 mL) and the mixture heated to 90°C to give a solution. A solution of 5-bromo-2-furaldehyde (10.0 g, 57 mmol) in DMF (50 mL) was added and heating continued overnight. The solution was evaporated, the residue dissolved in water (50 mL) and 2M hydrochloric acid added to pH 3. The resulting solid was collected, washed with water, then dried overnight in a desiccator over $P_2O_5$ to give 2-(5-formylfuran-2-ylthio)nicotinic acid (13.0 g, 92% yield).
m/z 250 (M+H), 248 (M-H).

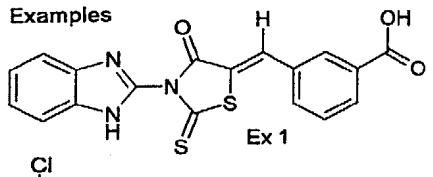
**Intermediate 6. 6-(5-Formylfuran-2-ylthio)nicotinic acid**

6-(5-Formylfuran-2-ylthio)nicotinic acid was prepared from 6-mercaptonicotinic acid and 5-bromo-2-furaldehyde according to the method for **Intermediate 5.**
m/z 250 (M+H), 248 (M-H).

**General Procedure for the Preparation of Examples.**

To a solution of the azole or barbiturate analogue of formula 2 (1.0 mmol) in boiling acetic anhydride (0.5 ml) was added NaOAc (5 mg), followed by a solution of the aldehyde of formula 3 (1.0 mmol) in hot acetic anhydride (0.5 ml). The solution was heated for 10 minutes, then cooled. The residue was triturated with diethyl ether, the solid collected, washed with diethyl ether and dried. The solid was suspended in water (1 ml) overnight, collected, washed with water and dried overnight in a desiccator over $P_2O_5$ to give the target compound of formula 1. Compounds were analysed by LCMS and $^1$H NMR.

Examples



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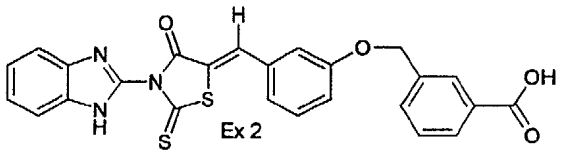

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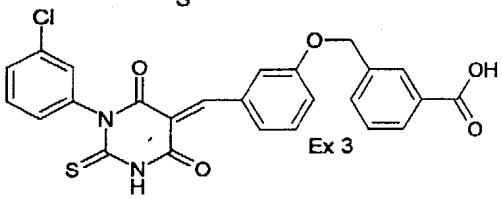

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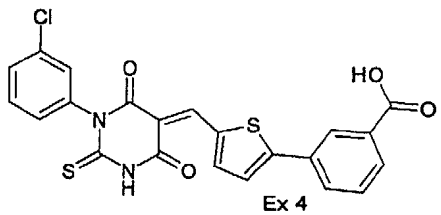

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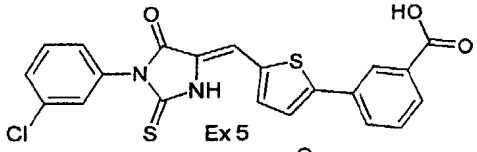

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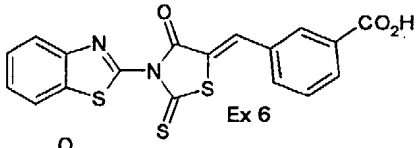

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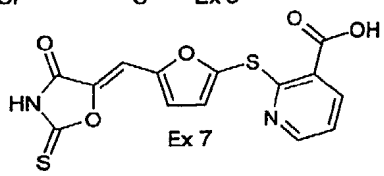

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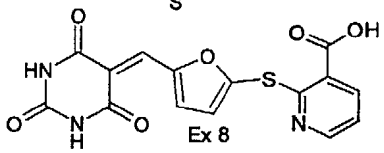

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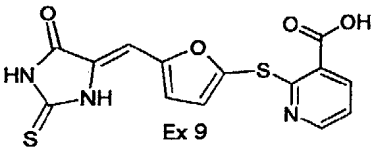

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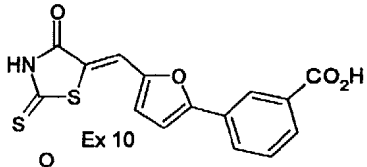
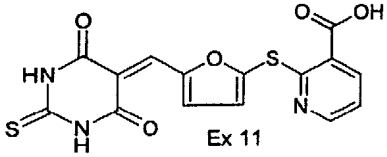


Ex 10



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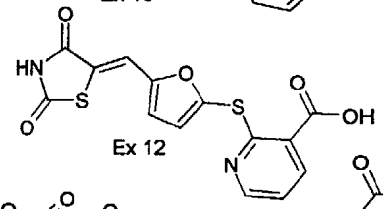

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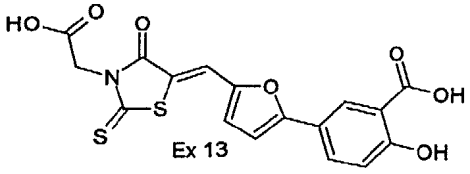

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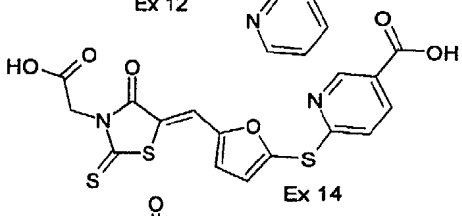
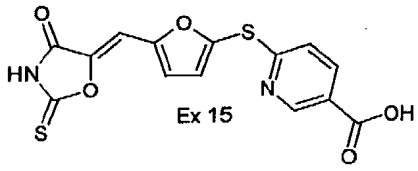
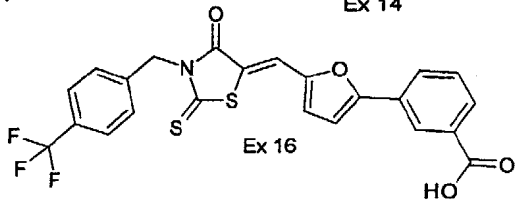


Ex 14



Ex 15



Ex 16

**Procedure for determining concentration of compound necessary to reduce the measured enzymatic activity of phosphopantetheine adenylyltransferase to half its control activity ($IC_{50}$)**

The inhibitory effect of a compound on PPAT can be measured by determining the difference in the amount of the product of the reaction released in the absence and presence of the compound. The reaction catalysed by PPAT is the transfer of the adenosine monophosphate moiety of ATP to 4-phosphopantetheine or an analogue thereof, generating the products dephosphoCoenzyme A, or an analogue thereof, and inorganic pyrophosphate.

In Webb, Proc. Nat. Acad. Sci. (USA), 1992; 89: 4884 – 4887, there is described an assay for the measurement of phosphate using the chromogenic substrate 2-amino-6-mercapto-7-methylaminopurine ribonucleoside (methyl thioguanosine). Phosphate was found to cleave this nucleoside in a reaction catalysed by purine nucleoside phosphorylase, generating ribose 1-phosphate and the corresponding free base, 2-amino-6-mercapto-7-methylaminopurine (methylthioguanine, MTG). Conversion of the nucleoside to MTG generates a readily monitored spectrophotometric signal at 360 nm. This assay was later extended by Lloyd et al, Nucleic Acids Research, 1995: 23: 2886-2892, to measure inorganic pyrophosphate by incorporating inorganic pyrophosphatase in the assay to generate inorganic phosphate which can then be assayed as described above.

**A Preparation of enzyme (PPAT)**

*Staphylococcus aureus* PPAT may be prepared from an overproducing strain of *E. coli* that harbours the gene encoding Staphylococcal PPAT on a multicopy plasmid. After growth, cells are harvested by centrifugation, and resuspended in 20 mM Tris-HCl buffer pH 8.0 containing 5 mM dithiothreitol (Buffer 1). Cells are broken by sonication and cell debris is removed by centrifugation. Ammonium sulphate (5.24 g/20 ml) is added to the supernatant to give 45% saturation, and the insoluble material is removed by centrifugation. More ammonium sulphate (1.38 g/20 ml) is added to the supernatant to give 55% saturation. The resulting precipitate is collected by centrifugation, re-dissolved in Buffer 1 and dialysed against Buffer 1.

The dialysed supernatant is then applied to a HiLoad™ Q (Amersham Pharmacia Biotech) ion-exchange column. PPAT is eluted by applying a gradient of NaCl (from 0 M to 1 M in Buffer 1. Fractions containing PPAT activity are combined, ammonium sulphate is added to give a final concentartion of 1.2 M, then the solution is applied to a HiLoad™ Phenyl-Sepharose (Amersham Pharmacia Biotech) hydrophobic interaction chromatography column. PPAT is eluted by applying a decreasing gradient (from 1.2 M to 0 M) of ammonium sulphate. Fractions containing PPAT activity are combined, then dialysed against 20 mM citrate buffer pH 5.5 containing 5 mM dithiothreitol (Buffer 2). The solution is then applied to a Sephacryl™ S-100 gel filtration column (Amersham Pharmacia Biotech) and eluted in Buffer 2. Fractions containing PPAT activity are dialysed into Buffer 1 for storage.

**B Measurement of enzymatic activity**

A reaction was carried out to measure phosphate production from the enzyme-coupled system, in the presence and absence of compounds. The reaction assay comprised 0.0023 units PPAT (where 1 unit is sufficient to catalyse the conversion of 1 micromole of substrate per minute per ml). The substrate for PPAT was 4-phosphopantetheine (100 μM) and ATP was also present in the reaction mix at a concentration of 100 μM. If present, the compound was added as a DMSO solution, so that the final DMSO concentration is 1% v/v.

Phosphate release was measured using the spectrophotometric assay as disclosed in Webb, *vide supra*.

**C Measurement of $IC_{50}$**

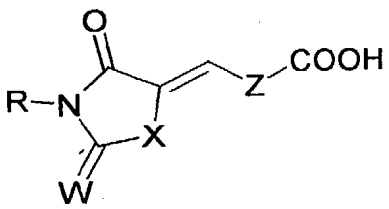
The inhibitory effect of a compound can be described by an $IC_{50}$ value, that is the concentration of inhibitor at which half (50%) inhibition of the maximal (100%) inhibition occurs. $IC_{50}$ values were determined by measuring the extent of inhibition over a range of concentrations of the compound, preferably a range where the degree of inhibition varied from no inhibition (0%) to complete inhibition (100%). The $IC_{50}$ value can be estimated from a plot of % inhibition against concentration of inhibitor, or can be calculated using data fitting programs, such Grafit (Elsevier) or EnzFitter (Biosoft).

**Results of $IC_{50}$ determinations**

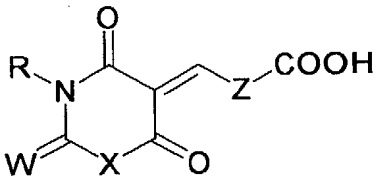
| Example | *Staphylococcus aureus* PPAT $IC_{50}$ (μM) |
|---|---|
| 1 | 3.2 |
| 2 | 3.3 |
| 3 | 4.7 |
| 4 | 13.2 |
| 5 | 11.2 |
| 6 | 1.6 |
| 7 | 0.68 |
| 8 | 12.9 |
| 9 | 1.8 |
| 10 | 15.2 |
| 11 | 7.0 |
| 12 | 3.7 |
| 13 | 7.7 |
| 14 | 7.3 |
| 15 | 1.2 |
| 16 | 9.4 |

**Claims**

1. A compound, for therapeutic use, of Formula 1



Formula 1a



Formula 1b

wherein W is S or O; X is NH, S or O; Z is one or more phenyl or heterocyclyl rings (optionally substituted by $C_{1-6}$ alkyl, halogen, hydroxy, alkoxy, nitro and trifluoromethyl) optionally separated by a spacing group $(Y)_n$ where Y is selected from $CH_2$, O, NH, S, S(O), $S(O)_2$ and n = 0 to 6; and R is hydrogen, a phenyl or heterocyclyl ring (optionally substituted by $C_{1-6}$ alkyl, halogen, hydroxy, alkoxy, nitro and trifluoromethyl) optionally separated by a spacing group $(Y)_n$ where Y is selected from $CH_2$, O, NH, S, S(O), $S(O)_2$ and n = 0 to 6, alternatively, R is of the form $(Y)_nCOOH$.

2. A compound of claim 1, independent of use, excluding :

3-(5-{(E)-[3-(3-chlorophenyl)-4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene]methyl}-2-furyl)benzoic acid

3. A compound of claim 1 where R is benzothiazole, m-chlorophenyl, p-(trifluoromethyl)benzyl, benzimidazole, hydrogen or $CH_2COOH$; X is NH, S or O; W is S or O and Z = phenyl, thiophene directly bound to phenyl, furan directly bound to phenyl, furanSph or $phOCH_2ph$.

4. A compound of claim 1, selected from:

3-{(Z)-[3-(1H-benzimidazol-2-yl)-4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene]methyl}benzoic acid

3-({3-[(Z)-(3-[1H-benzimidazol-2-yl]-4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]phenoxy}methyl)benzoic acid

3-[(3-{(E)-[1-(3-chlorophenyl)-4,6-dioxo-2-thioxotetrahydropyrimidin-5(2H)-ylidene]methyl}phenoxy)methyl]benzoic acid

3-(5-{(E)-[1-(3-chlorophenyl)-4,6-dioxo-2-thioxotetrahydropyrimidin-5(2H)-ylidene]methyl}thien-2-yl)benzoic acid

3-(5-{(Z)-[1-(3-chlorophenyl)-5-oxo-2-thioxoimidazolidin-4-ylidene]methyl}thien-2-yl)benzoic acid

3-{(Z)-[3-(1,3-benzothiazol-2-yl)-4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene]methyl}benzoic acid

2-({5-[(Z)-(4-oxo-2-thioxo-1,3-oxazolidin-5-ylidene)methyl]-2-furyl}thio)nicotinic acid

2-({5-[(2,4,6-trioxotetrahydropyrimidin-5(2H)-ylidene)methyl]-2-furyl}thio)nicotinic acid

2-({5-[(Z)-(5-oxo-2-thioxoimidazolidin-4-ylidene)methyl]-2-furyl}thio)nicotinic acid

3-{5-[(Z)-(4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]-2-furyl}benzoic acid

2-({5-[(4,6-dioxo-2-thioxotetrahydropyrimidin-5(2H)-ylidene)methyl]-2-furyl}thio)nicotinic acid

2-({5-[(Z)-(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]-2-furyl}thio)nicotinic acid

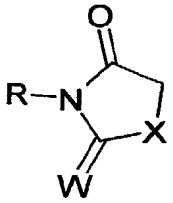
5-(5-{(Z)-[3-(carboxymethyl)-4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene]methyl}-2-furyl)-2-hydroxybenzoic acid

6-[(5-{(Z)-[3-(carboxymethyl)-4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene]methyl}-2-furyl)thio]nicotinic acid

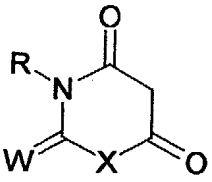
6-({5-[(Z)-(4-oxo-2-thioxo-1,3-oxazolidin-5-ylidene)methyl]-2-furyl}thio)nicotinic acid

3-[5-((Z)-{4-oxo-2-thioxo-3-[4-(trifluoromethyl)benzyl]-1,3-thiazolidin-5-ylidene}methyl)-2-furyl]benzoic acid

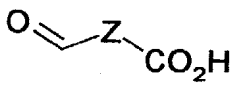
5. A procedure for preparing compounds of the invention comprising the reaction of a azole or barbiturate analogue of the formula 2a or 2b with an aldehyde of formula 3, wherein W, X, Z and R are as defined previously, preferably in boiling acetic anhydride as solvent, containing a catalytic amount of sodium acetate.




Formula 2a




Formula 2b




Formula 3

6. A pharmaceutical composition comprising as an active ingredient a compound of any preceding claim, together with a carrier or diluent.

7. Use of a compound of any of claims 1 to 4, for the manufacture of a medicament for the treatment of a bacterial infection.

8. The use of claim 7, wherein the infection is caused by a gram positive organism.

9. The use of claim 8, wherein the organism is *S. aureus*.

**Application No:** GB 0207410.2
**Claims searched:** 1-9

**Examiner:** Stephen Quick
**Date of search:** 27 June 2003

## Patents Act 1977 : Search Report under Section 17

**Documents considered to be relevant:**

| Category | Relevant to claims | Identity of document and passage or figure of particular relevance |
|---|---|---|
| X | 1, 2 & 6 at least | WO 01/93841 A2 (PROLIFIX) & Chemical Abstracts, abstr no 136:31669, see abstract and compound RN 292640-23-4 |
| X | 1, 2 & 6 at least | WO 00/18747 A1 (ROCHE DIAGNOSTICS) & Chemical Abstracts, abstr no 132:265191, see abstract and compound RN 263333-42-2 |
| X | 1, 2 & 6 at least | Bollettino Chimico Farmaceutico, 1997, Vol. 136(8), pages 561-567 & Chemical Abstracts, abstr no 132:273866, see abstract and compounds RN 185987-27-3 & 185987-28-4 |
| X | 1, 2 & 6 at least | JP 07/173143 A2 (WAKAMOTO PHARMA) 11.07.1995 & Chemical Abstracts, abstr no 123:228175, see abstract and compounds RN 168549-37-9, 168549-38-0, 168549-39-1, 168551-06-2, 168551-07-3, 168551-08-4, 168551-10-8, 168551-15-3, 168551-17-5, 168551-18-6, 168551-19-7, 168551-20-0 & 168551-21-1 |
| X,E | 2 & 6 at least | WO 02/50024 A2 (SMITHKLINE BEECHAM) 27.06.2002, see pages 1 (lines 25-29), 5 (lines 31-33) & 13 (last two compounds, which are compounds 13 & 14 on page 10) |
| X | 2 at least | Farmatsevtichnii Zhurnal (Kiev), 1983, Vol. (6), pages 32-34 & Chemical Abstracts, abstr no 100:191772, see page 33 (compounds IV & VI) |

Categories:

| | | | |
|---|---|---|---|
| X | Document indicating lack of novelty or inventive step | A | Document indicating technological background and/or state of the art. |
| Y | Document indicating lack of inventive step if combined with one or more other documents of same category. | P | Document published on or after the declared priority date but before the filing date of this invention. |
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INVESTOR IN PEOPLE

**Application No:** GB 0207410.2
**Claims searched:** 1-9

**Examiner:** Stephen Quick
**Date of search:** 27 June 2003

**Field of Search:**

Search of GB, EP, WO & US patent documents classified in the following areas of the UKC[V]:

Worldwide search of patent documents classified in the following areas of the IPC[7]:

The following online and other databases have been used in the preparation of this search report:

CAS ONLINE